REMARKS

The Claim Amendments

Claims 7-20, 23-36 and 42-44 are pending. Claims 1-6, 21-22, and 37-41 stand withdrawn.

Applicants have amended claims 7-10, 12, 14, 16, 20, 26, 28-30, 32, 33, 35, 42-44. Applicants have amended claims 7-9 and 42-44 to improve their form and to recite proper antecedent basis. Support for amended claims 9 and 42 can be found, e.g., on page 1, lines 1-9; page 4, line 31 to page 5, line 19; page 6, lines 25-30, page 13, lines 11-19; and in claim 2 as originally filed. Support for amended claims 7, 8 and 43 can be found, e.g., on page 1, lines 1-9; page 4, lines 5-22; page 6, lines 25-30 and in claim 5 as originally filed. Support for amended claim 44 can be found, e.g., on page 1, lines 1-9; page 6, lines 5-22; page 6, lines 25-30; page 13, lines 11-19; and in claim 6 as originally filed. The back reference claim numbering has also been adjusted accordingly. Applicants have also amended claims 12, 14 and 16 to correct improper multiple dependencies, as requested by the Examiner.

These claim amendments are made expressly without waiver of applicant's rights to pursue any canceled subject matter in divisional or other related application(s) claiming benefit from this application. None of the amendments adds new matter. Their entry is requested.

The Office Action

The Examiner acknowledged applicants' elections of Group III and the selected species. He has examined claims 7-20, 23-36 and 42-44 on the merits.

Priority Claim

The Examiner has stated that the application upon which priority is claimed (US Provisional Application 60/198,069) fails to provide adequate support under 35 U.S.C. §112 for the claims of this application. The Examiner states that the '069 application does not provide support for the "genetic package" genus that is currently claimed, as well as majority of species that would fall within the scope of the broad genetic package genus. The Examiner has therefore deemed the effective filing date of this application to be April 17, 2001. Applicants traverse. The priority document provides adequate support for the claims of the application. Solely to advance prosecution, applicants have rendered moot the Examiner's objection to the "genetic package genus" by amending claims 7-9 and 42-44, the independent claims pending in this application, to recite a library of phage, rather than genetic packages. *See,* applicants remarks to the Examiner's enablement rejection under 35 U.S.C. §112, first paragraph, *infra*.

Information Disclosure Statement

Applicants acknowledge the Examiner's consideration of the documents submitted in the January 15, 2002, April 10, 2002 and September 2, 2003 Information Disclosure Statements.

Claim Objections

The Examiner has objected to claims 12-17 as being in improper multiple dependent form. Applicants have amended the claims to remove any improper multiple dependencies.

Claim Rejections

35 U.S.C. §112, first paragraph – Enablement

The Examiner has rejected claims 7-20, 23-36 and 42-44 under 35 U.S.C. §112, first paragraph. The Examiner states that while the specification is enabling for a library of phage particles that display antibody fab/scfv where said particles are produced using class II-S restriction enzymes that cleave the encoding DNA, the Examiner alleges that it is not enabling for the production of *any* genetic package that expresses *any* polypeptide/protein using *any* restriction enzyme to cleave *any* type of nucleic acid (i.e., RNA). The Examiner states that even within a narrow subset of applicants' claims, the art is recognized to be diverse and unpredictable. The Examiner also states that the specification provides no guidance with the use of retroviruses, which the claims would encompass. The Examiner also contends that the specification provides no guidance on how to protect the displayed proteins from digestion by proteases, aggregation, misfolding, blocked secretion and/or the use of Cys-containing mutants. Applicants traverse in part.

As suggested by the Examiner, applicants have amended all of the independent claims, now pending in this application (claims 7-9 and 42-44) to recite a library of phage, rather than genetic packages. Support for this amendment can be found throughout the specification, *e.g.*, at page 1, lines 15-17. As suggested by the Examiner, applicants have also amended these claims to recite the type of nucleic acid as DNA. Support for this amendment can be found throughout the specification, *e.g.*, at page 2, lines 10-25; and page 10, lines 17-20.

Applicants disagree with the Examiner's assertion that they do not provide guidance for the use of any restriction enzyme other than Type II-S restriction sites. Applicants teach the production of libraries that express peptides, polypeptides and/or proteins using restriction enzymes that are not Type II-S, i.e., those that cleave outside of their recognition sequence at defined positions to one side. Rather, the restriction enzymes used in claim 7, cut the DNA at defined positions within their recognition sequences. They are Type II, not Type II-S, restriction enzymes. Applicants have amended claim 7 to recite that the restriction enzyme is a Type II enzyme. The preferred Type II restriction enzymes are specifically recited in claims 28 and 29. Applicants thus enable the production of libraries using restriction enzymes that are not Type II-S restriction enzymes to cleave DNA.

Applicants also disagree with the Examiner's assertion that the specification does not provide guidance for the use of any peptide, polypeptide and/or protein or how to protect such displayed proteins from digestion from proteases, aggregation, misfolding, blocked secretion and/or the use of cys-containing mutants. Applicants teach a library comprising a collection of phage that display a member of a diverse family of peptides, polypeptides or proteins that collectively display *at least a portion* of the diversity of the family, a multiplicity of the displayed peptides, polypeptides or proteins being encoded by nucleic acid sequences produced by the methods of this invention. This teaching does not necessitate that each and every one of the family members will be displayed on the phage and thus protected from the above intracellular events. It may well be the case that some of the peptides, polypeptides or proteins undergo digestion by proteases, aggregation, misfolding, etc, in the phage.

However, as acknowledged by the Examiner on page 8 of the Office Action, a strong bias against particular DNA sequences is unlikely. Thus, while it may be the case that not all variants are displayed on the phage, at least a portion of them will be. The claims are therefore fully enabled for a library characterized by at least a portion of the diversity of the family. In view of the amendments and arguments, applicants request that the Examiner reconsider and withdraw the enablement rejection.

35 U.S.C §112, second paragraph – Indefiniteness

The Examiner has rejected claims 7-9, 23-36 and 42-44 under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner states that there is insufficient antecedent basis for "the region in which cleavage is desired" in claims 7-9, 42-44 and all claims that depend therefrom.

Accordingly, applicants have amended claims 7-9 and 42-44 to correct the antecedent basis and recite "a region in which cleavage is desired". Applicants have also amended these claims to improve their form and to further describe the desired location for the cleavage, i.e., the desired location is a location that removes all unwanted 5' nucleotides from the DNA. Support for these amendments is described, *supra*. These amendments overcome the rejection.

The Examiner states there is insufficient antecedent basis for "the two strands" in claims 7-9 and 42-44. Accordingly, applicants have amended claims 7-9 and 42-44 to recite "the DNA and the oligonucleotide". This obviates the rejection.

The Examiner has rejected claim 10 for insufficient antecedent basis for "the nucleic acids". Accordingly, applicants have amended independent claims 7-9 and

42-44 to recite the "nucleic acid sequences". This provides the necessary antecedent basis for claim 10. Similarly, the Examiner has objected to using "nucleic acid" and/or "nucleic acids" in claims 7-10, 18, 20 and 42-44, when used in conjunction with oligonucleotide. The Examiner states this use of terminology is confusing. Applicants believe this rejection has been largely obviated by the above amendments, which now use the term nucleic acid sequences or a DNA including one of those sequences. This distinguishes the sequences and DNA from the recited oligonucleotides.

The Examiner also states there is insufficient antecedent basis in claims 7-9 and 42-44 for reciting "the oligonucleotide" in step (i). Accordingly, applicants have obviated this objection by amending claims 7-9 and 42-44 to replace reference to "the" oligonucleotide with "a" and to recite "wherein said" oligonucleotide as the next back reference.

In view of these amendments, applicants request that the Examiner reconsider and withdraw the indefiniteness rejections.

35 U.S.C. §102/103 – Anticipation and Obviousness

Suzuki

The Examiner has rejected claims 7-13, 16-20, 23-36 and 42-44 under 35 U.S.C. §102(a) as being anticipated by, or, in the alternative, under 35 U.S.C. §103(a) as obvious over Suzuki et al., Biochem. Biophys. Res. Commun, 271:240-243 (2000) ("Suzuki").

The Examiner states that Suzuki discloses a library comprising a collection of genetic packages that display a member of a diverse family of peptides,

polypeptides, or proteins and collectively display at least a portion of the diversity of the family, wherein genetic packages are phage, diverse family of peptides, polypeptides, or proteins are human anti-double stranded DNA IgG Fab.

The Examiner acknowledges that Suzuki does not disclose that the same method steps as recited in claims 7-13, 16-20, 23-36 and 42-44, form the libraries. The Examiner, however, contends that the products appear to be the same as those recited in the instant claims. Specifically, the Examiner states that Suzuki discloses the features of the claims, including human anti-double stranded DNA IgG Fab including heavy/light chains of claims 10-13, 16 and 17, the disease Lupus of claims 18-19, and peripheral blood cells of claim 20. The Examiner contends that the libraries of Suzuki therefore meet all of the limitations of the claimed libraries except for the product by process limitations and would thus either render anticipate or render obvious the claimed library, since one would expect the library to be the same "no matter how it was synthesized and/or prepared" (page 14 of the Office Action). Applicants traverse, and in view of the claim amendments made in this response request reconsideration.

Amended claims 7-20, 23-36 and 42-44 are directed to a library comprising a collection of phage that display a member of a diverse family of peptides, polypeptides or proteins and collectively display at least a portion of the diversity of the family, a multiplicity of the displayed peptides, polypeptides or proteins being encoded at least in part by nucleic acid sequences produced by the specific methods described in this application. The libraries of the amended claims are not anticipated or rendered obvious by Suzuki.

The libraries of amended claims 7-9 and 42-44 (and the claims that depend therefrom) are patentably different from the libraries of Suzuki. As described in the "Background of the Invention" Section of this application, the libraries of this invention that display members of a diverse family of peptides, polypeptides and proteins are prepared using amplification primers.

In one conventional method, those primers are complementary to sequences "native" to the DNA being used to make the library. See, e.g., Suzuki, citation 15 (Kang et al.) As such, they prevent maximum diversity from being achieved because the native DNA that binds to the primer and is amplified from it cannot be substantially diverse. Rather, diversity is blocked or suppressed by the primer. For example, the primer only amplifies those DNAs to which it is substantially complementary. This biases the library. And, the amplification primer suppresses any diversity in the complementary region. Both lead to less than optimally diverse libraries. In the libraries of this invention, primers are used that are external to the native DNA to be amplified, i.e., they bind to synthetic sequences 5' to the diversity causing DNA sequences to be fully amplified without any bias or suppression. Thus, the libraries of this invention are different from those previously prepared using internal primers in that they are unbiased and maintain maximum diversity. *See,* page 2, line 10 to page 3, line 12; page 13, line 28 to page 14, line 5.

In another conventional method of making libraries using primers, the amplification primers are external to the "native" DNA that is being used to make the library. In this situation, maximum diversity may be achieved. However, there is still a problem, the amplified sequence must be restricted for cloning and expression. Such

restriction, when done at the site of the amplification primer, typically leaves extraneous DNA sequences 5' to the "native" diverse DNA to be cloned and expressed. These sequences may interfere with cloning and expression of the sequences in the library. *See*, page 3, lines 13-24.

In the libraries of this invention this problem is avoided. As described in the specification and recited in the claims, there are two alternative embodiments for effecting appropriate cleavage. The first uses a single-stranded oligonucleotide that is complementary to the amplified DNA and internal to its diversity. Using temperature to maintain the amplified DNA single-stranded, the oligonucleotide forms a Type II restriction site at the closer location and operates at the elevated temperature to remove the unwanted 5' nucleotides for the amplified DNA. The second uses a partially double-stranded oligonucleotide. The single-stranded region is complementary to the single-stranded amplified DNA. The double-stranded region of the oligonucleotide carries a Type II-S recognition site such that upon cleavage a restriction cut removes all of the unwanted 5' nucleotides from the amplified, diverse DNA. *See*, page 4, lines 1–4; page 16, line 25 to page 17, line 3. In addition, in accordance with this invention, a restriction site can be chosen that occurs in substantially all of the amplified DNAs. *See*, page 29, line 31 to page 30, line 14. Thus, the library is more uniform in construction.

For these reasons then, the claimed libraries are not anticipated or rendered obvious by the libraries of Suzuki. The claimed libraries have maximum diversity. And, they do not contain 5' sequences that are deleterious to expression. None of the prior libraries in the art has both characteristics.

Applicant therefore requests that the Examiner reconsider and withdraw this objection.

Burton

The Examiner has rejected claims 7-18, 20, 23-36 and 42-44 under 35 U.S.C. §102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. §103(a) as obvious over Burton et al., International Publication WO 94/07922 ("Burton").

The Examiner states that Burton discloses a library comprising a collection of genetic packages that display a member of a diverse family of peptides, polypeptides, or proteins and collectively display at least a portion of the diversity of the family, wherein phagemid libraries are human anti-HIV antibodies.

The Examiner acknowledges that Burton does not disclose that their libraries are formed by the same method steps as recited in claims 7-18, 20, 23-36 and 42-44, but the Examiner contends nonetheless products of Burton appear to be the same as those recited by the instant claims, regardless of their method of manufacture. Specifically, the Examiner states that Burton discloses the features of the claims, including the display of human antibodies with light/heavy chains including Fab and FR1 regions of claims 10-17, the autoimmuno-deficiency syndrome of claim 18, spleen and bone marrow of claim 20. The Examiner concludes that the process limitations of the instant claims do not appear to provide any patentable weight tot he claimed invention since one of ordinary skill would expect the library of genetic packages to be the same "no matter how it was synthesized" (page 17 of the Office Action). Applicants traverse, in view of the claim amendments and the above arguments.

The libraries of Burton, do not anticipate or render obvious the claimed libraries. Burton uses amplification primers that are complementary to the "native" DNA being used to make the library. *See, e.g.,* page 80. Burton, therefore, prevents maximum diversity from being achieved because the "native" DNA that binds to the primer cannot be substantially diverse.

In sum, the amended claims are not anticipated or obvious over the documents cited by the Examiner because they allow, by choice of appropriate restriction site and primer, extensive and maximal diversity to be captured. They also remove all unwanted 5' nucleotides leading to consistent expression and display. *See, e.g.,* page 18, lines 25-33. Nothing in Suzuki or Burton suggests the construction of a library with such diversity or the other unexpected attributes of the library disclosed in the present application. Applicants respectfully request that the Examiner reconsider these rejections.

Double Patenting

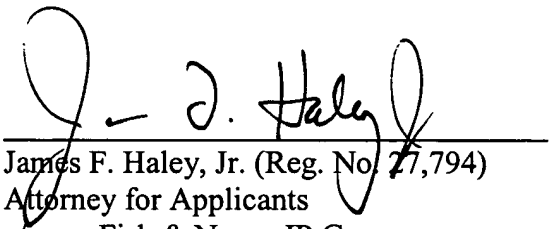
The Examiner has provisionally rejected claims 7-20, 23-36 and 42-44 as being unpatentable under the doctrine of obviousness-type double patenting over claims 1-116 of co-pending application no. 10/045,674. The Examiner states that although the claims are not identical, they are not patentably distinct from each other because the claims are either anticipated by, or would have been obvious over, the reference claims. The rejection is provisional because the conflicting claims have not yet been patented.

Applicants are willing to file one or more terminal disclaimers, in compliance with 37 C.F.R. §1.321(c), to obviate any obviousness-type double patenting rejection, upon allowance of any of the conflicting claims in this application.

CONCLUSION

Applicants request that the Examiner consider the above remarks, withdraw all outstanding rejections, and allow the pending claims.

Respectfully submitted,



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